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PULMONARY ADAPTATION TO HIGH ALTITUDE

ANNUAL SUMMARY REPORT - YEAR 04
(September 1, 1980 - July 10, 1981)

Jerome A. Dempsey, Ph.D.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The work accomplished during year 04 of our contract was aimed at: (1) animal studies which defined the effects of chronic hypoxia on CNS neurotransmitter metabolism and on cerebral tissue (H+) regulation and related these to ventilatory acclimatization; and (2) human studies which examined the nature of ventilatory periodicity during sleep in hypoxia and the effects of heavy exercise on pulmonary gas exchange. The following general conclusions are warranted from this past year's efforts. (continued on back)			

a. Brain intracellular $[H^+]$ (in dogs) is very closely regulated in short-term hypoxia secondary mainly to increased brain metabolic acid production.

b. Metabolic acid production in brain increases in acute hypoxia, but shows "adaptation" with chronic hypoxia, i.e. either remaining constant or showing substantial reduction with time. This cerebral metabolic acid production is critically dependent upon the attending respiratory alkalosis, especially in moderate levels of hypoxemia.

c. Ventilatory acclimatization to or deacclimatization from chronic hypoxia do not show clear relationships to cerebral tissue metabolic acid production or--presumably--cerebral fluid acidification.

d. Monoamine neurotransmitter synthesis and turnover in the CNS show adaptation to chronic hypoxia (in the rat). We found no relationship of this metabolism to ventilatory acclimatization, nor did we find that pharmacologic manipulation of these monoamines changed ventilatory acclimatization. Dopamine concentration changes in the carotid body were striking and progressive with time in hypoxia, and their functional relevance needs further study.

e. "Instability" in human breathing patterns in hypoxia was quantified in sleep, working and exercising states. Periodicity occurred consistently in all subjects, appeared soon after the onset of hypoxia (during sleep), was relieved by acute restoration of normoxia and diminished by low levels of CO_2 and occurred in all Non-REM sleep stages. Marked variability was evident among subjects in their "sensitivity" to development of periodic breathing in hypoxia.

f. Arterial hypoxemia during heavy exercise showed a high incidence in fit subjects at sea level. Its' occurrence was critically dependent upon the level of alveolar PO_2 , suggesting a diffusion limitation to pulmonary gas exchange. Marked variability existed among individuals in their susceptibility to exercise-induced hypoxemia.

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ANNUAL PROGRESS REPORT
(Year 04 - September 1, 1980-July 1, 1981)

Studies completed during contract year 04 were aimed at defining relationships between brain metabolism and ventilatory acclimatization to chronic hypoxia, explaining the nature and some of the mechanisms controlling instability in breathing pattern during sleep, and clarifying the contributions of alveolar P_0_2 and alveolar-capillary diffusion to the arterial hypoxemia we have observed during heavy work at sea-level and moderate altitudes.

SUMMARY OF PROGRESS TO DATE

I. CNS Metabolism in Hypoxia--Regulation and Relationship to Ventilatory Acclimatization

A. Brain Tissue $[H^+]$ and Metabolic Acid Production

Our work is now completed in this project (see Peiligrino, Musch, and Dempsey, Brain Res., 1981; and Musch et al., 1981, FASEB abstract). The study in anesthetized dogs compared various methods for measuring intra-cellular pH (pH_i) in various brain regions and determined pH_i regulation in response to various combinations of hypoxia and hypocapnia imposed over five hours. Major findings included: 1) the heterogeneity in pH_i and metabolic acid production throughout the brain under all conditions; 2) the much tighter regulation of intra-cellular pH--relative to that in plasma or bulk CSF--during hypocapnia and/or hypoxia; 3) cerebral pH_i in any of the regions or by any of the methods showed no change over 5 hours of hypoxic hypocapnia (simulated 4300 m, $PaCO_2 \sim 25$, $PaO_2 \sim 45$ mmHg). pH_i was elevated in the initial hour of moderate hypocapnia, but returned to normal after 5 hours; 4) increased cerebral metabolic acid production (mainly lactate) was critical to pH_i regulation in the initial hour of hypoxia or hypocapnia, but were unchanged with further (time-dependent) regulation of pH_i suggesting a key role for transmembrane transport of H^+ during this period; 5) brain extracellular fluid space fell during hypocapnia and hypoxemia and intracellular fluid rose. This cellular swelling was possibly secondary to an osmotic effect of increased metabolic acid production; 6) by comparing different methods for pH_i measurement we were also able to estimate the amount of disequilibrium in $[HCO_3^-]$ between bulk CSF and interstitial fluid. We found this disequilibrium only in the initial hour of hypoxic hypocapnia, i.e. by 5 hours of continued hypoxic hypocapnia there was no evidence of any disequilibrium (CSF:ISF).

Our second study used awake rats studied over the time-course (2 hrs to 7 days) of acclimatization to and deacclimatization from chronic hypoxia to moderate and severe hypoxia (4 to 6000 m, PaO_2 55 to 28 mmHg, $PaCO_2$ 35 to 15 mmHg). Major findings were: a) cerebral (cortex and brain stem) metabolic acid concentrations (i.e. primarily lactic acid) were increased 2 to 3 fold in chronic hypoxia and in most cases remained elevated following acute return to normoxia during which time the animal continued to hyperventilate; b) the time-course of these changes varied with the severity of hypoxia, always showing an elevation in acute hypoxia with no further change over

1 to 7 days of moderate hypoxia but with a significant fall over 3 days of severe hypoxia; c) the attending hypocapnia in hypoxia was critical to the changes in cortex and brain stem metabolic acid production, i.e. when iso-capnia was maintained in acute hypoxia the increase in cerebral lactate was either prevented (moderate hypoxia) or reduced (severe hypoxia) and if PaCO_2 was elevated to control levels during acute return to normoxia in the acclimatized animal, brain tissue lactate also returned to normal; d) intra-cellular pH (estimated by the creatine phosphokinase equilibrium technique) in brain stem and cortex was unchanged from control in all conditions and durations of hypoxia and/or hypocapnia, except in very severe acute hypoxia, during which cerebral pH_i was significantly acid to control under both hypocapnic and iso-capnic conditions.

These data have several general implications concerning adaptation to chronic hypoxia. In particular, they show the brain's metabolic adaptability during acclimatization wherein metabolic acid production either stabilizes or is greatly reduced with time in hypoxia and intra-cellular pH homeostasis is maintained in all chronic states of acclimatization. Further, the critical importance of hypocapnia (and alkalosis?) to cerebral metabolic acid production and to pH_i regulation was clearly demonstrated. Hypoxemia, *per se*, contributed significantly to these metabolic changes only at extreme altitudes. Thirdly, the data also speaks to the question of cerebral interstitial fluid (ISF) acidification in hypoxia and its recently postulated role in ventilatory acclimatization (Fencl, 1979).

1. The dog data suggests that CSF:ISF disequilibrium (for $[\text{HCO}_3^-]$ and $[\text{H}^+]$) may not exist beyond the very early stages of hypoxic exposure. (Clearly our method and that of Fencl's (1979) for determining this "disequilibrium" differ greatly and a critical analysis and comparison of both techniques is indicated).
2. Cerebral tissue metabolic acid production does not provide a source for increased acidification of cerebral ISF commensurate with an increasing ventilation with time in hypoxia--quite the opposite.
3. Differing degrees of hypoxia all produced a similar degree of ventilatory acclimatization (acute to chronic hypoxia) but quite different time-dependent changes in cerebral metabolic acid production.

Finally, these data, taken together with previous findings, show a highly complex profile of cerebral fluid acid-base regulation during acclimatization to chronic hypoxia i.e. arterial plasma and bulk CSF increase in alkalinity, cerebral ISF $[\text{H}^+]$ (implied from metabolic acid changes) stays constant or decreases in acidity and intra-cellular pH remains unchanged for the most part or returns from a mildly acid to normal level with time. Exactly how medullary chemoreceptors may respond to this profile of $[\text{H}^+]$ in cerebral fluids--or how one might estimate the ionic composition of the chemoreceptor environment--appears as anything but straightforward.

B. Monoamine Metabolism in the CNS and Carotid Body and Relationships to Ventilatory Control and Acclimatization

Two types of studies have been completed which address these questions:

1. The site of action of serotonin (5-HT)--on ventilatory control and its interaction with other chemical stimuli and exercise were studied in awake-intact and carotid chemoreceptor denervated goats. Our previous work in rats was confirmed in the intact goat by showing that serotonin depletion (via parachlorophenylalanine, PCPA) caused chronic hyperventilation and respiratory alkalosis. The carotid-denervated animal showed an identical response (to the intact) confirming a CNS site of action of 5HT depletion on eupneic ventilation, and the ventilatory effects of acute hypoxia, hyperoxia, CO₂ breathing, and exercise were strictly additive to those of 5HT depletion. We also studied 5HT repletion in awake and anesthetized rats using 5HTP (the biosynthetic precursor to serotonin). This caused a mild hyperventilation in the awake rat but caused a marked hypoventilation in the halothane anesthetized rat. These anesthetic effects explain some of the existing discrepancies in the literature (see below) and stress the critical importance of studying ventilatory control in the awake state, where our studies clearly show that CNS 5HT exerts a strong inhibitory influence on eupneic ventilation and that this inhibition is present in a variety of physiologic states.
2. Monoamine Neurotransmitter Metabolism and Ventilatory Control During Acclimatization to Hypoxia--was studied in male, Sprague-Dawley rats (300-350 g) housed in a hypobaric chamber (BP = 450 Torr) for up to 7 days. The levels of norepinephrine (NE), dopamine (DA), and serotonin [5-hydroxytryptamine (5HT)] were measured--after extraction and HPLC--by electrochemical detection in whole brain, brain stem, and carotid bodies. Monoamine turnover was estimated by the average of: a) the buildup in monoamine levels 1 hour following inhibition of monoamine oxidase; and b) the depletion in monoamine levels 1 hour following inhibition of tryptophan and tyrosine hydroxylases. Pertinent findings were as follows:
 - (a) Levels of monoamines in CNS: In whole brain the levels of all three monoamines appear to be transiently reduced on acute exposure to hypoxia. This is significant for NE at 1 hour and DA at 5 hours hypoxia.
 - (b) Turnovers of monoamines in CNS: In whole brains the turnover of 5HT is transiently reduced after 1 and 5 hours hypoxia and return to normal levels by 1 day [This agrees with the previously published work of Davis and coworkers (197)]. Based on indirect evidence, Davis and coworkers have postulated a transient fall in NE turnover during hypoxia. Our data does not support this conclusion. We find that NE turnover is unaffected by hypoxia. Both DA and 5HT turnovers were elevated after 7 days hypoxia and 1 hour acute return to normoxia.
 - (c) Levels in carotid bodies: A 4- to 5- fold increase occurred in carotid body DA after 7 days hypoxia with a further increase after 1 hour return to normoxia. NE is moderately elevated in carotid bodies after 7 days hypoxia, but carotid body 5HT levels are unaffected. The fact that the carotid body monoamines do not change in concert supports the premise that this is a specific effect of prolonged hypoxia on carotid body DA.

This observed adaptation of nervous tissue monoamines to prolonged hypoxia lends itself to several interpretations. First, there are 2 lines of evidence which argue that there is no significant role for CNS monoamines in ventilatory acclimatization to hypoxia. 5HT turnover with time of adaptation to hypoxia changes opposite to the ventilatory effects we have shown through pharmacological depletion of 5HT. We would expect 5HT turnover to go down when ventilation increases during hypoxic adaptation, but 5HT turnover returns to normal.

In further studies in rats, we have shown that pharmacological depletion of any of these monoamines does not alter the rat's time course of ventilatory acclimatization to and deacclimatization from chronic hypoxia. These findings do not confirm the postulate of Millborn et al. (1981) who showed that 5HT depletion prevented the continued increase in ventilation following carotid sinus nerve stimulation in anesthetized, prolonged cats. Either their animal model may not be a suitable simulation of chronic "acclimatization" or the anesthetic effects may account for these differences in findings.

Finally, others have shown in ponies and goats that carotid bodies are clearly involved in ventilatory acclimatization to hypoxia (Bisgard, 1980). The adaptation of carotid body dopamine that we have demonstrated may be involved in this relationship, and we will test this hypothesis further.

II. Ventilatory Control and Stability During Sleep in Hypoxia

Several more studies were completed in this area (Berssenbrugge, 1980; Iber, 1981). First, we have now completed our computerization of this analysis of breathing stability, whereby all ventilatory data is analyzed on a breath-by-breath basis, over 20 to 30 minute periods in a given physiologic condition and "stability" is quantitated according to apnea number and length, distribution of V_T , inspiratory flows, \dot{V}_E , f, ribcage and abdominal contributions to V_T , and HbO_2 saturation, and the "cyclical" nature of groups of breathing patterns is quantitated.

Secondly, we have studied five more normal subjects--awake and asleep--over four days at 4300 m altitude in the hypobaric chamber--while awake at rest, during 30 mins of mild exercise, and during all sleep stages. These data are still under analysis, but have already yielded the following findings: 1) Overall ventilatory acclimatization--documented by measurements of \dot{V}_E and 50 to 60 samples of arterialized acid-base status per night--from acute (mins to hrs) over 4 days of hypoxia was identical at rest awake, during exercise, and during all sleep stages. These data question a significant role in acclimatization for influences from suprapontine areas (higher CNS) and question the basic premise (Tenney, 1971) that these influences have an interactive effect on chemical ventilatory control. 2) Apnea, cyclical changes, and periodic breathing were marked during all NREM sleep stages but much less evident in REM and barely measurable--although clearly present--while awake at rest or during work. The apneas were of the "central" non-obstructed variety. 3) Periodicity in all sleep stages was affected by a number of perturbations and conditions: a) acute hyperoxia removed it;

b) very low levels of inhaled CO₂ (often with no detectable change in arterial PCO₂) greatly alleviated it, and c) time in hypoxia clearly decreased this instability, i.e. the periodicity was most marked during the initial 1-5 hours of hypoxia, was lessened over the next 24 hours and then diminished greatly over the final 48 hours at 4300 m. Increase in "quality" sleep time (stages III, IV, NREM) and loss of sleep-related symptoms such as morning headache, extreme fatigue, etc., seemed to coincide with reduction in breathing "instability" and maintenance of higher levels of arterial HbO₂ saturation.

A third series of studies completed with the awake chemodenervated goat model also speaks to the postulated role of chemoreception and shifts in central vs. peripheral chemoreceptor influences on breathing stability (Cherniack et al., 1973 and 1979). For example, the carotid-chemoreceptor denervated goat (relative to intact) tended to show wide distributions of VT, $\dot{V}E$, etc., at both rest and exercise. Acute hypoxia in the denervated animal tended to show further slight increases in "instability." On the other hand steady-state cisternal perfusion with alkaline and acid mock CSF in the intact goat produced the expected hyper- or hypo-ventilation but did not affect ventilatory "stability." While considerable work remains on this topic this combination of human and animal data are beginning to define the role of chemoreceptor contribution in the production of breathing instability, and thus far clearly question the postulated role for a dominance of peripheral over central chemoreceptor influences as a precipitating factor and implicate a role for cerebral hypoxia, *per se*.

III. Exercise Gas Exchange and Ventilatory Response

Based on some of our earlier observations of significant arterial hypoxemia in well-conditioned athletes during very heavy work, this study sought to more clearly define the incidence and exercise conditions necessary for this hypoxemia and to examine the possibility that it might be attributed to a limitation in alveolar-capillary diffusion. Two major findings have resulted from this year's work.

First, the incidence of a reduced arterial PO₂ (-15 to 40 mmHg < Rest) during heavy work at sea-level in health seems to be fairly high (17 of 25 subjects). The work load must be "heavy" (>75% Max $\dot{V}O_2$) to induce this hypoxemia in most subjects. Even mild levels of acute hypoxia (simulating 7000-8000 feet) will either cause hypoxemia in those who do not show it in normoxia and will cause much more severe arterial hypoxemia in those who already demonstrate it in normoxia. The nature of the work--or at least the ventilatory response to the work--may be a factor. That is, the hypoxemia and O₂ desaturation is evident in the initial 45 seconds of the exercise and is either sustained or progresses over the next 3 to 4 minutes. This pattern holds for either walking up a steep grade or running on the level. However, if--at slightly lower work levels--the work is prolonged (>15 mins) and a greater ventilatory response is obtained, the hypoxemia either doesn't occur or is minimized.

The second major finding here was obtained in 15-20 repreated tests in just a few subjects (N = 6). We sought to vary the alveolar PO₂ in small increments or decrements and thereby change the alveolar to mean-capillary diffusion gradient for O₂. Whether this was accomplished by greater alveolar

ventilation (via Helium breathing) or by slightly raising or lowering the inspired PO₂ (FIO₂ .17 to .24) the same result was obtained, i.e. the exercise-induced hypoxemia was highly sensitive to the prevailing alveolar PO₂ (Fig. 1). This effect on arterial PO₂ of changing the alveolar PO₂ occurred very quickly during exercise, was readily reversible, and highly reproducible (Fig. 2). The data are clearly indicative of a diffusion limitation in the healthy person during heavy exercise at sea level. Even more relevant is the fact that this limitation becomes specifically evident with major effects on arterial O₂ content at even mild levels of high altitude.

IV. Publications - Contract Year 04 (September 1, 1980 - July 1, 1981).

a) Manuscripts Published (or in Press)

1. Forster, H.V. and Dempsey, J.A. "Control of Breathing." In: Ventilatory Adaptations in Regulation of Breathing, Vol. II, (edited by T. Hornbein), Springer Verlag, 1981 (In Press).
2. Pelligrino, D.A., Musch, T.I. and Dempsey, J.A. "Interregional differences in brain intracellular pH and water compartmentation during acute normoxic and hypoxic hypocapnia in the anesthetized dog." Brain Res., 214:387-404, 1981.
3. Dempsey, J.A. "Limiting role of the pulmonary system in exercise capacity." Proceedings of the Canadian Assoc. Sports Sciences Symposium on Limiting Factors in Exercise (Toronto, Canada, October, 1980) (In Press).
4. Dempsey, J.A., Berssenbrugge, A., Musch, T. and Skatrud, J. "O₂: CO₂ interactions in hypoxia: ventilatory control." Proceedings of Hypoxia Symposium II (Banff, Canada, January, 1981) (In Press).
5. Bateman, N.T., Musch, T.I., Smith, C.A. and Dempsey, J.A. "Problems with the gas-calibrated PCO₂ electrode." Resp. Physiol., 41:217-226, 1980.
6. Iber, C., Berssenbrugge, A., Skatrud, J., and Dempsey, J. "Effects of slow-wave sleep on the ventilatory response to flow resistive loads." J. Appl. Physiol. (In Press, 1981).
7. Dempsey, J.A. and H.V. Forster. "Mediation of ventilatory adaptations." Physiological Reviews (In Press).
8. Dempsey, J., Hanson, P., Sanyer, O., and Claremont, A. "Failure of pulmonary O₂ transport in endurance athletes." In: Exercise in Health and Disease (eds. F. Nagle and H. Montoye). C. Thomas, Illinois, 1981, p. 68-78.
9. Vidruk, E. and J. Dempsey. "Peripheral and central nervous mechanisms controlling exercise-induced breathing patterns." Exercise and Sports Sciences Reviews, (Amer. College Sports Med. Series), Vol 8, pp. 129-148, 1981.

b) Abstracts

1. Berssenbrugge, A., Dempsey, J., Skatrud, J., and Iber, C. "The effect of chronic hypoxia on breathing pattern in wakefulness and sleep." The Physiologist 23(4):727, 1980.

2. Iber, C., Berssenbrugge, A., SKatrud, J., and Dempsey, J. "Human ventilatory responses to inspiratory resistive loading during wakefulness and slow wave sleep." The Physiologist 23(4):724, 1980.
3. Musch, T.I., Smith, C.A., Bateman, N.T., Mitchell, G.S. and Dempsey, J.A. "Relative contributions of hypoxemia and alkaloisis to brain metabolic acid production during acclimatization to hypoxia." Fed. Proc. 40(3):1116, 1981.
4. Olson, E.B., Jr., Dempsey, J.A., McCrimmon, D.R., and Vidruk, E.H. "Monoamine neurotransmitter metabolism during acclimatization to hypoxia." Fed. Proc. 49(3):1914, 1981.
5. Smith, C.A., Mitchell, G.S., Jameson, L.C. and Dempsey, J.A. "Ventilatory response of goats to treadmill exercise: speed vs. grade." Fed. Proc. 40(3):1141, 1981.
6. Dempsey, J.A., Hanson, P.E. and Mastenbrook, S.M. "Arterial hypoxemia during heavy exercise in highly trained runners." Fed. Proc. 40(3):932, 1981.

V. Military Significance

Adaptability to the physiologic stresses of high altitude hypoxia clearly requires appropriate compensatory changes at the tissue level. Our basic work has essentially described the nature and some of the mechanisms underlying these metabolic changes--in both mitochondrial and neurotransmitter metabolism in cerebral tissue.

Sleep-related problems are commonly linked to symptoms of acute mountain sickness. Clearly, the ventilatory periodicity prominent during sleep in hypoxia affects the quality of sleep and thus the level of hypersomnolence and fatigue experienced during waking states--particularly during the initial few days at altitude. Our work on this problem provides the first comprehensive description of this problem and provides insight into means of its alleviation.

Work capacity at sea level and high altitudes is critically dependent on oxygen delivery to working skeletal muscle. Our work thus far has identified exercise-induced hypoxemia under certain exercise conditions in a large percentage of healthy individuals at sea level, and has demonstrated the sensitivity of this hypoxemia to even small changes in inspired (and alveolar) PO₂. Susceptibility to this problem, which seems to be predictable even at sea level, may be a critical determinant of exercise performance at high altitudes.

VI. Facilities

No new major facilities were added in year 04. The most significant change in our laboratory operation has been in computerized data acquisition and analysis.

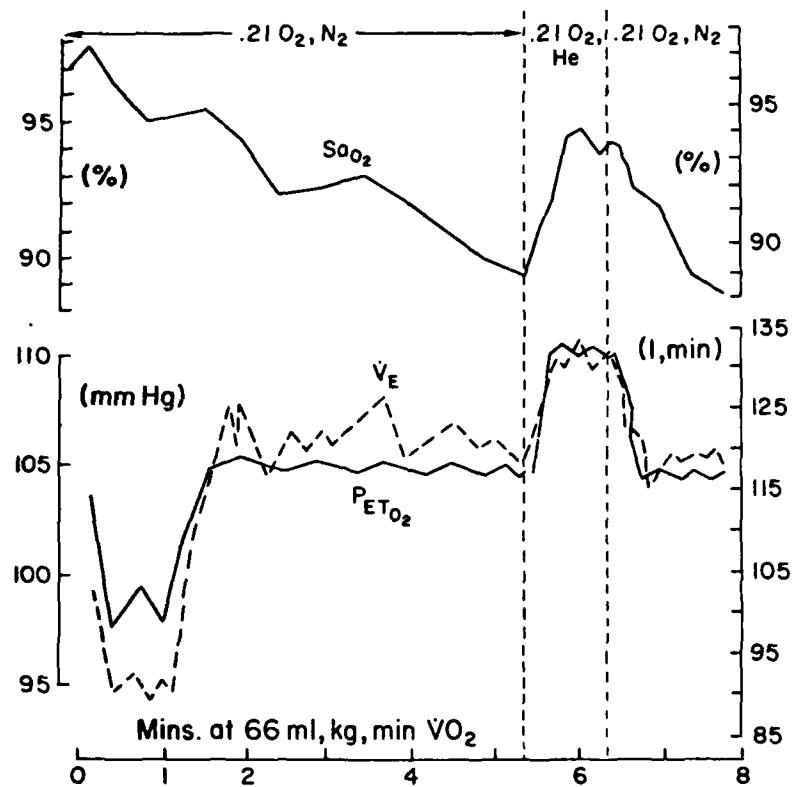


FIGURE 1. Effects of Helium breathing during heavy exercise on ventilatory response (\dot{V}_E), alveolar P_{O_2} (P_{ETO_2}), and on arterial O_2 saturation (SaO_2). Note the progressive desaturation breathing room air, the immediate effects of $He:O_2$, $PETO_2$, and hence SaO_2 ; and the immediate reversability of these effects upon return to room air breathing.

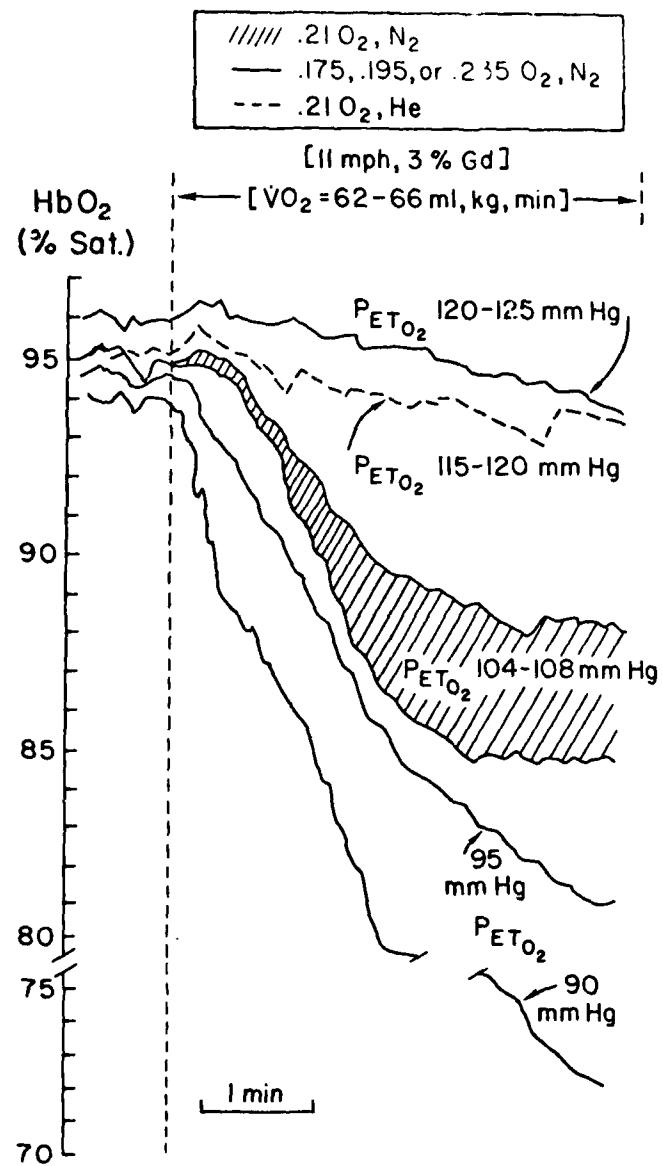


FIGURE 2. Summary of 12 experiments defining the sensitive relationship between alveolar PO₂ and arterial HbO₂ saturation during heavy exercise in a single subject. Note: the desaturation in 4 experiments breathing room air (PETO₂ 104-108); the marked further desaturation at low FIO₂ (.175 to .195), and PETO₂ (90-95); and the prevention of desaturation with 7 to 20 mmHg increases in PETO₂ via Helium breathing or mildly increased FIO₂.

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